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# Transition Metal Complexes with Antipyrine-Derived Schiff Bases: Synthesis and Antibacterial Activity

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Additional information is available at the end of the chapter

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## Abstract

The increase of death rate, associated with infectious diseases, is directly linked to the bacteria that have multiple resistance to antibiotics. The lack of efficient medical treatment is the main cause of this problem. The synthesis of new antibacterial agents, through various methods, is, for sure, an emergency medical issue. Recent research focuses more and more on the synthesis of complexes of the transitional metals with ligands of Schiff-base type, as a result of the biological properties which they have. This article presents the synthesis of several complexes with base Schiff ligands, derived from 4-aminoantipyrine and in vitro research of their antibacterial activities. The new compounds were tested for their in vitro antibacterial activity against *Staphylococcus aureus* var. Oxford 6538, *Klebsiella pneumoniae* ATCC 100131, *Escherichia coli* ATCC 10536, and *Pseudomonas aeruginosa* ATCC 9027 strains. Based on the “in vitro” studies, we can say that ten of the complexes synthesized can be successfully used instead of streptomycin, where there is resistance to this antibiotic.

**Keywords:** 4-aminoantipyrine, Schiff bases, metal complexes, antibacterial agents, streptomycin

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## 1. Introduction

The synthesis of new antibacterial agents, through various methods, is, for sure, an emergency medical issue [1–3]. Schiff bases are important precursors for the synthesis of some bioactive compounds [4, 5]. Schiff bases have received considerable attention since the discovery of their antibacterial [6, 7], antifungal [8], anti-HIV [9, 10], anti-inflammatory [11], anticonvulsant [12, 13], antiviral [14], and anticancer properties [15–17]. The presence of the inimical grouping in these organic ligands plays an important part in manifesting these biological characteristics

[18–20]. Schiff bases can be regarded as promising antimicrobial agents. For example, N-(salicylidene)-2-hydroxyaniline proved efficiency against *Mycobacterium tuberculosis* H37Rv, exhibiting an MIC value of 8 µg/mL [21]. The 5-chloro-salicylaldehyde-Schiff base derivatives are efficient against *Pseudomonas fluorescens* (MIC=2.5–5.2 µg/mL), *Escherichia coli* (MIC=1.6–5.7 µg/mL), *Bacillus subtilis* (MIC=1.8 µg/mL), and *Staphylococcus aureus* (MIC=1.6 and 3.1 µg/mL), respectively, while the MIC values for the reference drug kanamycin against the same bacterial strains were 3.9 µg/mL [22]. Some of the isatin-derived Schiff bases have shown antibacterial activity against *Escherichia coli* NCTC 10418 (MIC=2.4 µg/mL), *Vibrio cholerae* non-01 (MIC=0.3 µg/mL), *Enterococcus faecalis* (MIC=1.2 µg/mL), and *Proteus shigelloides* (MIC=4.9 µg/mL). The MIC values for the reference drug sulfamethoxazole against the same bacterial strain were in the range of 312–5000 µg/mL. Therefore, these compounds were proven to be 1040-, 1040-, 4160-, and 1020-fold more potent than sulfamethoxazole [23, 24]. The studies run on the Schiff bases, derived from the isoniazid have allowed to identify a compound which has turned out to have a therapeutical effectiveness and safety, that is, 4000 times higher than that of isoniazid [25].

The morpholine-derived Schiff bases was effective against *Staphylococcus aureus* (MIC=20 µg/mL), *Micrococcus luteus* (MIC=32 µg/mL), *Streptococcus epidermidis* (MIC=17 µg/mL), *Bacillus cereus* (MIC=21 µg/mL), and *Escherichia coli* (MIC=16 µg/mL).

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety completely inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. MIC values for these compounds varied from 6.3 to 12.5 µg/mL, which are comparable to those obtained for the reference drug ciprofloxacin [26]. Lately, within the last couple of years, a special attention has been paid to the chemistry of the metal complexes of the Schiff bases. This is due to the chemical stability of the complexes as well as to the possibility of using them in the most varied fields. To a great extent, remarkable successes, in this field, have been obtained due to the various synthesis methods of the complexes. Recent research focuses more and more on the synthesis of complexes of the transitional metals with ligands of Schiff-base type, as a result of the biological properties which they have. In many cases, the conclusion has been that, through the coordination of the Schiff bases, to the metal ions, which are present in the biological systems, the biological activity of the respective Schiff base increases. A large number of Schiff bases and the corresponding metal complexes have proven antibacterial, antifungal, antitumor, and antileukemia activity [27–29].

Ever since it was synthesized [30], antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) has enjoyed a lot of attention due to its analgesic and antipyretic properties. The discovery of these properties has allowed for deeper research on antipyrine and its derivatives. Thus, 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (4-aminoantipyrine) was discovered, a derivative with analgesic action, antipyretic, anti-inflammatory, antibacterial, and antineoplastic [31, 32]. The derivatives of 4-aminoantipyrine are used in the synthesis of azo-colorant, in analytical chemistry for spectrophotometric determination of metal ions [33], in pharmacology, as an effective antitumor [34], analgesic [35], antiviral [36], anti-inflammatory [37], anticancer [38], and antimicrobial drugs [39–42].

Lately, the research has been conducted in order to get metal complexes with a wide range of biological activities and with the lowest level of toxicity. In this work, the synthesis of some complexes with base Schiff ligands is presented, derived from 4-aminoantipyrine and in vitro research of their antibacterial activities.

## 2. Experimental

### 2.1. Metal complexes with aminoantipyrine Schiff bases: structure and methods of synthesis

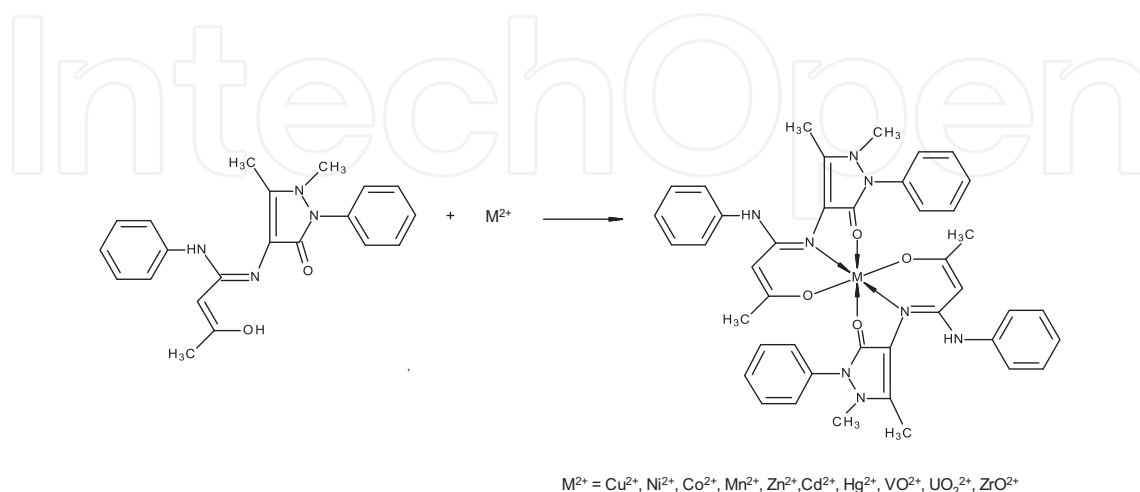
Complexes of Cu(II), Co(II), Ni(II), Zn(II), Mn(II), VO(II), and Fe(III) were prepared by direct reaction between Schiff base ligand and the corresponding metal salts.

The next Schiff bases were synthesized:

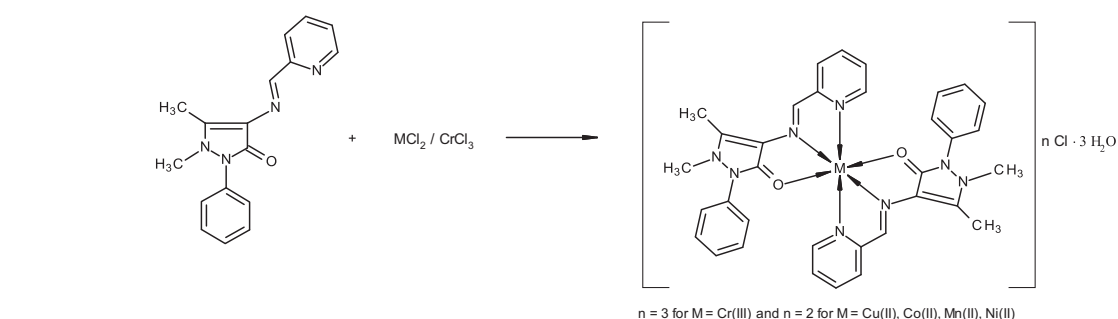
- 1-phenyl-2,3-dimethyl-4-(N- acetoacetanilide)-3-pyrazolin-5-one (**HL<sup>1</sup>**)
- 1,5-dimethyl-2-phenyl-4-(1-(pyridin-2-yl)ethylideneamino)-1H-pyrazol-3(2H)-one (**HL<sup>2</sup>**)
- 5-nitro-salicylidene-4-aminoantipyrine (**HL<sup>3</sup>**)
- 4-((E)-4-((E)-(4-chlorophenyl)diazenyl)-2-hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (**HL<sup>4</sup>**)
- 1-phenyl-2,3-dimethyl-4-(N-imidazole-2-carboxaldehyd)-3-pyrazolin-5-one (**HL<sup>5</sup>**)
- 4-(2-pyrrolylmethylideneamino)antipyrine (**HL<sup>6</sup>**)
- 4[(benzylidene)amino]antipyrine (**HL<sup>7</sup>**)
- 4[(cinnamalidene)amino]antipyrine (**HL<sup>8</sup>**)
- 4[(2-chlorobenzylidene)amino]antipyrine (**HL<sup>9</sup>**)
- 4-[(furan-2-ylmethylene)amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3Hpyrazol-3-one(**HL<sup>10</sup>**)
- 1-phenyl-2,3–dimethyl-4-(2-hydroxy-5-nitro-benzylideneamino)-3-pyrazolin-5-one (**HL<sup>11</sup>**)
- salicylidene-4-aminoantipyrine (**HL<sup>12</sup>**)
- salicylidene-4-aminoantipyrinyl-2-amino-3-hydroxypyridine (**HL<sup>13</sup>**)
- naphthylidene-4-aminoantipyrine (**HL<sup>14</sup>**)
- 5-[(E)-[(3Z)-3-[2-[(Z)-[4-[(E)-(3-hydroxy-4-nitro-phenyl)methyleneamino]-1,5-dimethyl-2-phenyl-pyrazol-3-ylidene]amino]phenyl]imino-1,5-dimethyl-2-phenyl-pyrazol-4-yl]iminomethyl]-2-nitro-phenol (**HL<sup>15</sup>**)
- 4-[(E)-[(3Z)-3-[2-[(Z)-[4-[(E)-(4-hydroxy-3-methoxy-phenyl)methyleneamino]-1,5-dimethyl-2-phenyl-pyrazol-3-ylidene]amino]phenyl]imino-1,5-dimethyl-2-phenyl-pyrazol-4-yl]iminomethyl]-2-methoxy-phenol (**HL<sup>16</sup>**)
- 3-salicylideneacetylacetone-2,4-di(imino-4'-antipyrinyl)pentane (**HL<sup>17</sup>**)
- 2,6-diformyl-4-methylphenol bis(4-amino-3-antipyrine) (**HL<sup>18</sup>**)
- 4,4'-(1E,1'E)-(1,1'-(pyridine-2,6-diyl)bis(ethan-1-yl-1-ylidene))bis(azan-1-yl-1-ylidene) bis (1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) (**HL<sup>19</sup>**)
- 3(3'-hydroxy-4'-nitrobenzalidene)-2,4-di(imino-4'-antipyrinyl)pentane (**HL<sup>20</sup>**)

### 2.1.1. Synthesis of the complexes with $HL^{1-5}$ ligands

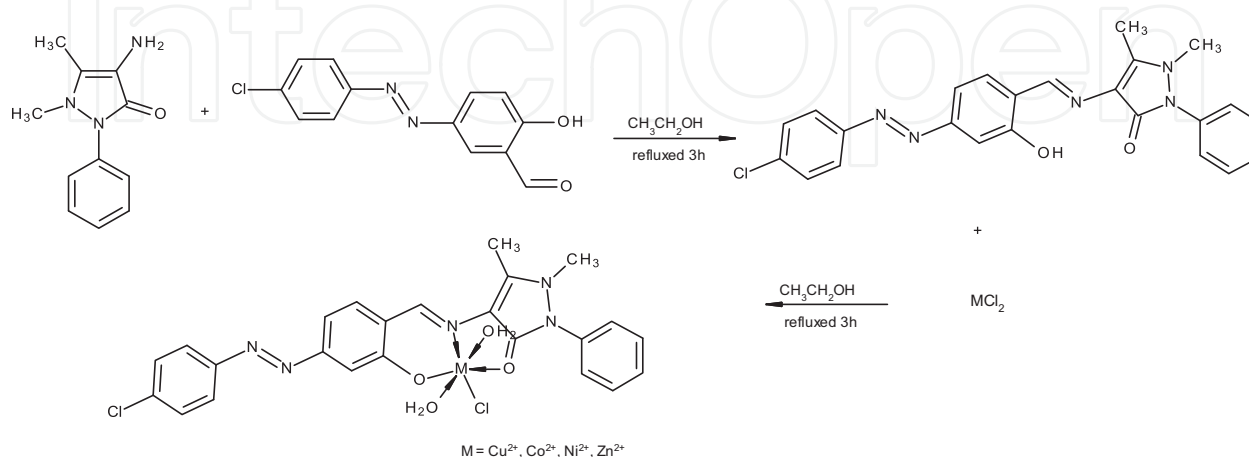
The metal complexes with these Schiff bases are obtained by adding a methanolic or ethanolic ligand solution to a solution of metal salt, in a molar ratio L:M=2:1 [43, 44] or 1:1 [45–47]. The mixture of reaction is refluxed for 2–5h or stirring for 12h. The precipitate is obtained that is filtered, washed with ether, methanol or ethanol, and dried *in vacuo* (**Figures 1–4**).



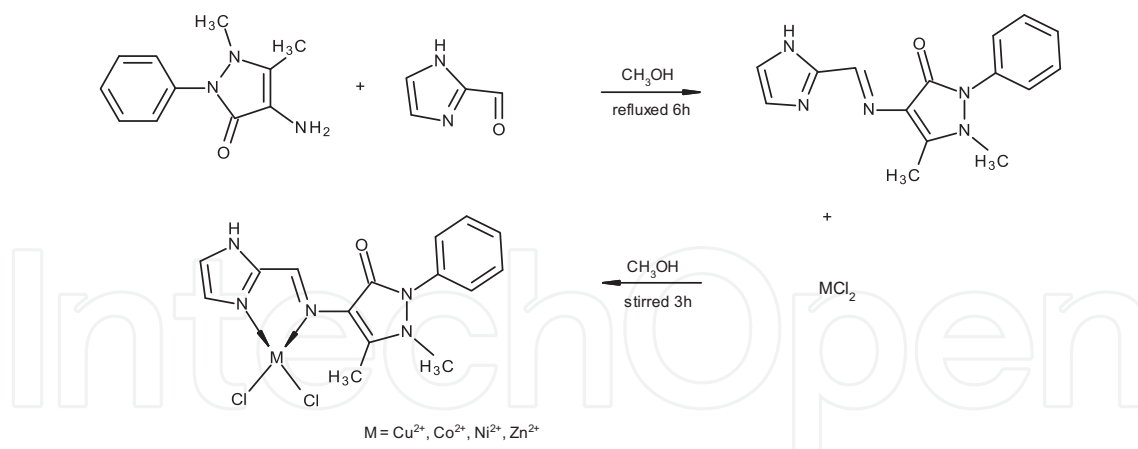
**Figure 1.** Scheme of synthesis of complexes with ligand  $HL^1$ .



**Figure 2.** Scheme of synthesis of complexes with ligand  $HL^2$ .



**Figure 3.** Scheme of synthesis of complexes with ligand  $HL^4$ .



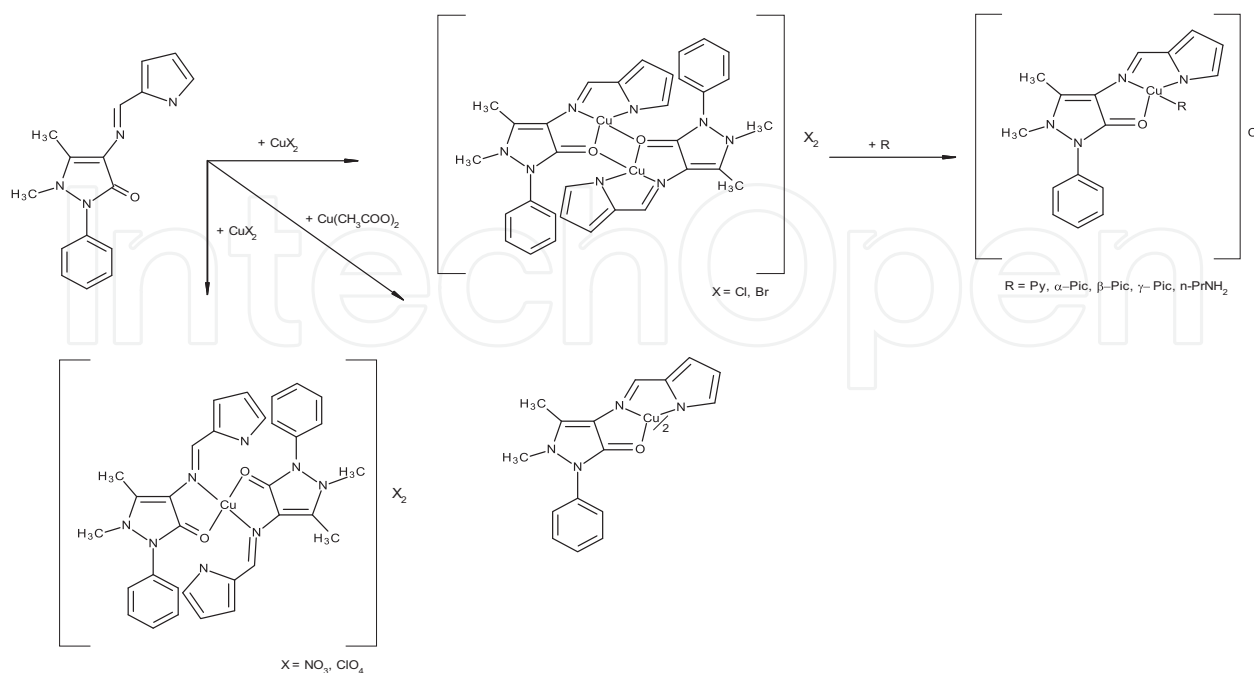
**Figure 4.** Scheme of synthesis of complexes with ligand **HL**<sup>5</sup>.

### 2.1.2. Synthesis of the complexes with ligands **HL**<sup>6–11</sup> and various co-ligands

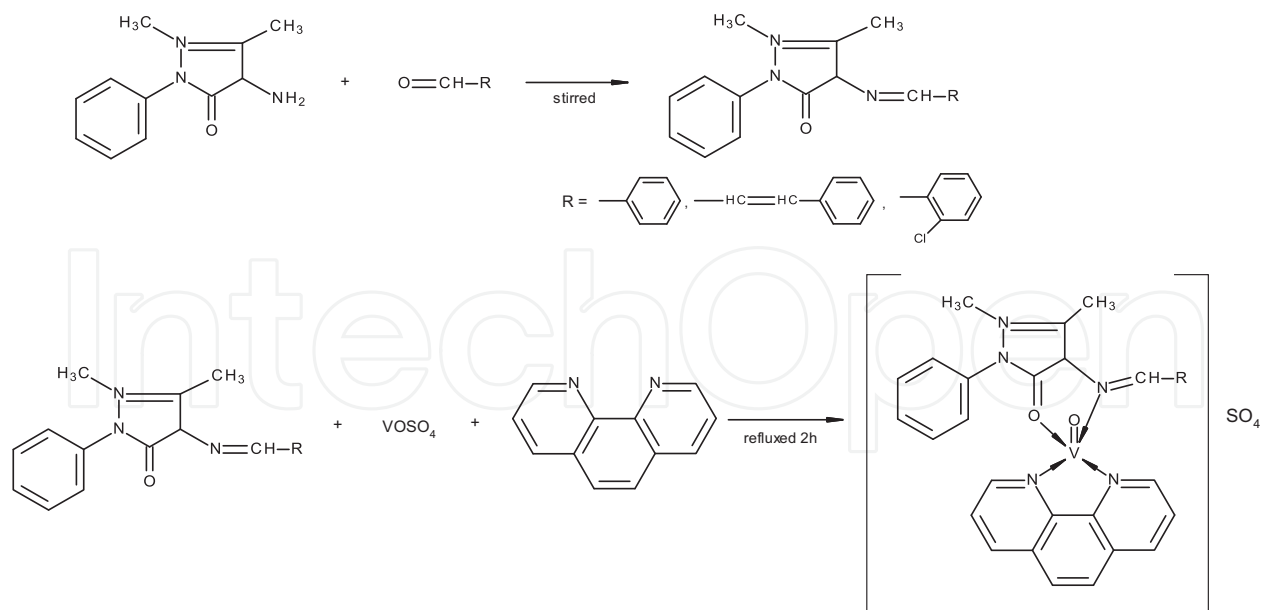
The metal complexes with ligands base Schiff **HL**<sup>6–11</sup> are obtained through three methods:

*Method 1.* Previously, the complex combination with the Schiff base is obtained to which the co-ligand is added ( $\alpha$ -picoline,  $\beta$ -picoline,  $\gamma$ -picoline,  $n$ -propylamine). After the complete precipitation, the solid compound is obtained that is filtered, washed with ether, and dried in the exicator (**Figure 5**) [48].

*Method 2.* The mixture of reaction which contains the alcoholic ligand solutions (the Schiff base and the co-ligand) and the alcoholic solution of metal salt is refluxed for 6–8h. After the concentration of the solution to a third of its volume, on the water bath, a precipitate is obtained which is filtered, washed with alcohol, and dried in vacuo (**Figure 6**) [49]; (**Figure 7**) [50, 51].



**Figure 5.** Scheme of synthesis of complexes with ligand **HL**<sup>6</sup>.



**Figure 6.** Scheme of synthesis of complexes with ligands **HL**<sup>7-9</sup>.

*Method 3.* By adding an ethanolic solution of Schiff base to a metal salt solution, in a molar ratio 1:1, a mixture is obtained which is refluxed for 3–8 h. An ethanol solution of co-ligand (amino acids; 1,10-phenanthroline; 2,2'-bipyridine; etc.) is added in the reaction environment, and the reflux is kept going on for another 1–3 h. The precipitate is obtained which is filtered, washed in ether, and dried in vacuo (**Figure 7**) [52, 53]; (**Figure 8**) [54].

#### 2.1.3. Synthesis of the complexes with ligands **HL**<sup>10, 12-14</sup> and various aromatic amine

The metal complexes with these Schiff bases are obtained through refluxing, lasting for 3–4 h of a mixture that contains the metal salt dissolved in ethanol and the ligand dissolved in the same solvent. The ligand can be previously obtained through two different methods (**Figure 9**) [55], respectively (**Figure 10**) [53, 56–58].

#### 2.1.4. Synthesis of the complexes with ligands **HL**<sup>15</sup> and **HL**<sup>16</sup>

The metal complexes with ligands Schiff bases **HL**<sup>15</sup> and **HL**<sup>16</sup> are obtained by treating a ligand solution with a solution of metal salt, in a molar ratio L:M=1:1. The mixture is refluxed for 5–6 h. After the concentration of the solution to a third of its volume, on the water bath, a precipitate is obtained which is filtered, washed with ether, and dried in vacuo (**Figure 11**) [59, 60].

#### 2.1.5. Synthesis of the complexes with ligands **HL**<sup>17-20</sup>

The metal complexes with Schiff base ligands **HL**<sup>17-20</sup> are obtained through treating a solution that contains the ligand dissolved in ethanol or acetonitrile with the solution of metal salt, in a molar ratio of L:M=1:1. The mixture is refluxed for 5–6 h (**Figures 12, 13**) [61–64] or, in other cases, even 12 h (**Figure 14**) [45]. The precipitation begins immediately or after the concentration of the solution to a third of its volume, on a water bath. The precipitate is obtained which is filtered, washed with ether, and dried in vacuo.



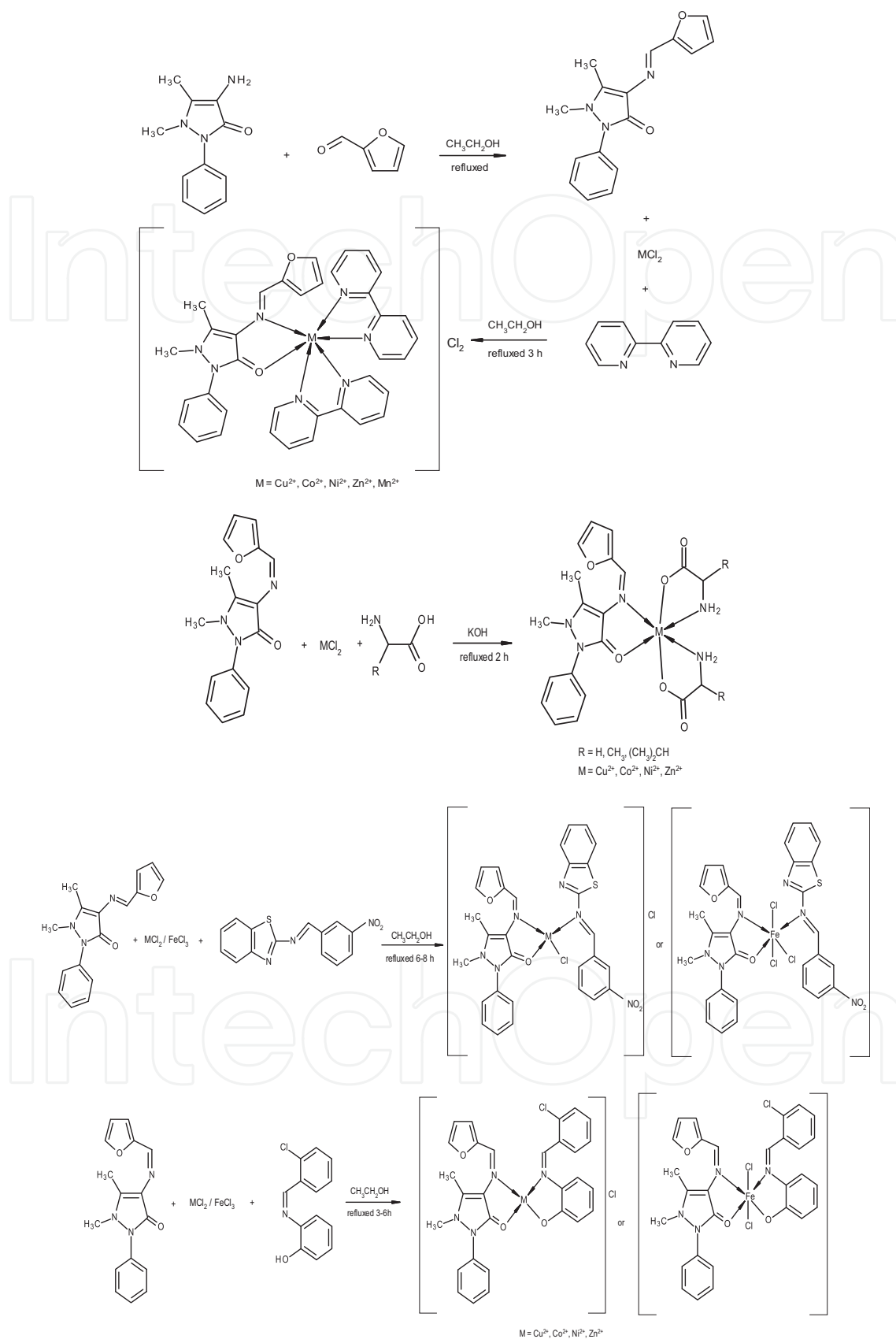
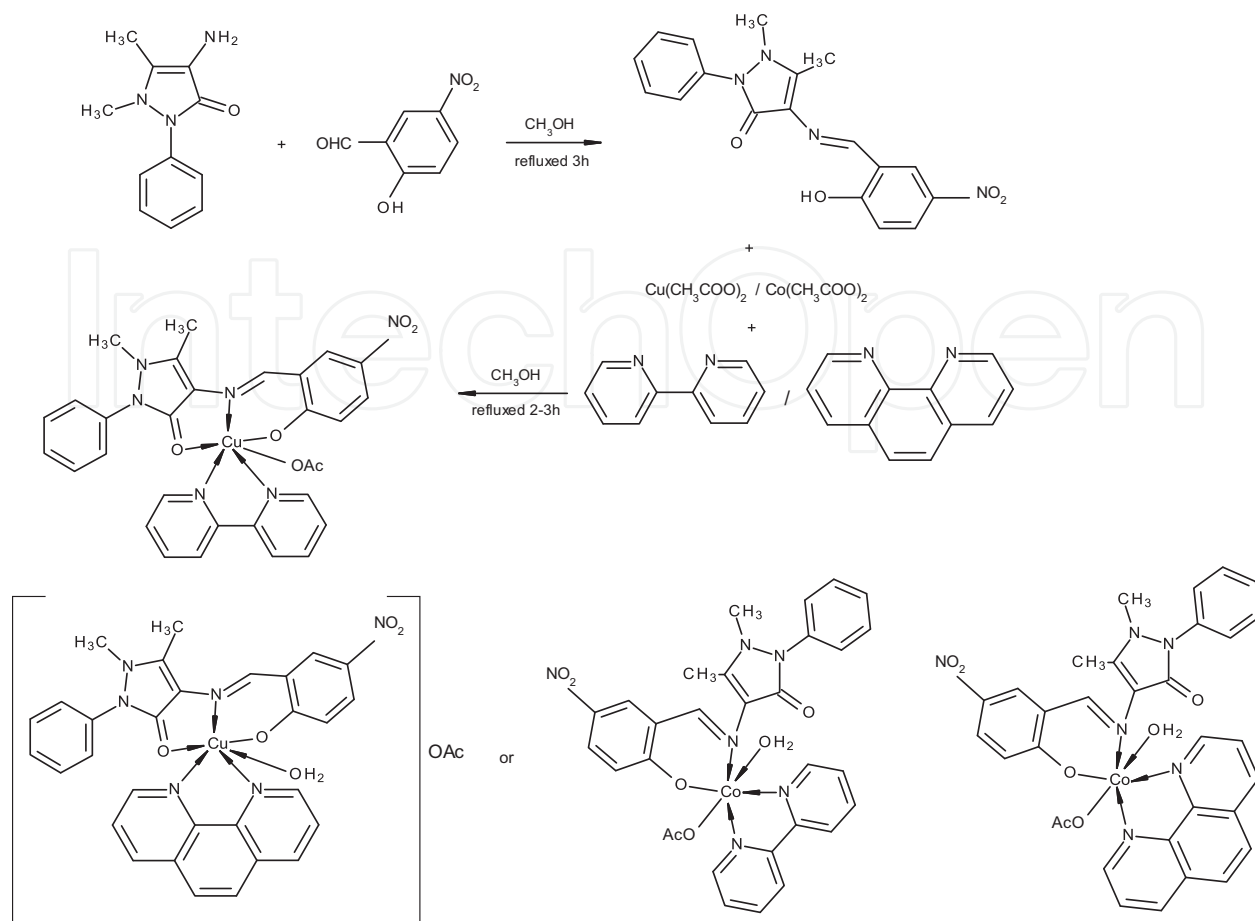


Figure 7. Scheme of synthesis of complexes with ligand HL<sup>10</sup>.





**Figure 8.** Scheme of synthesis of complexes with ligand **HL<sup>11</sup>**.

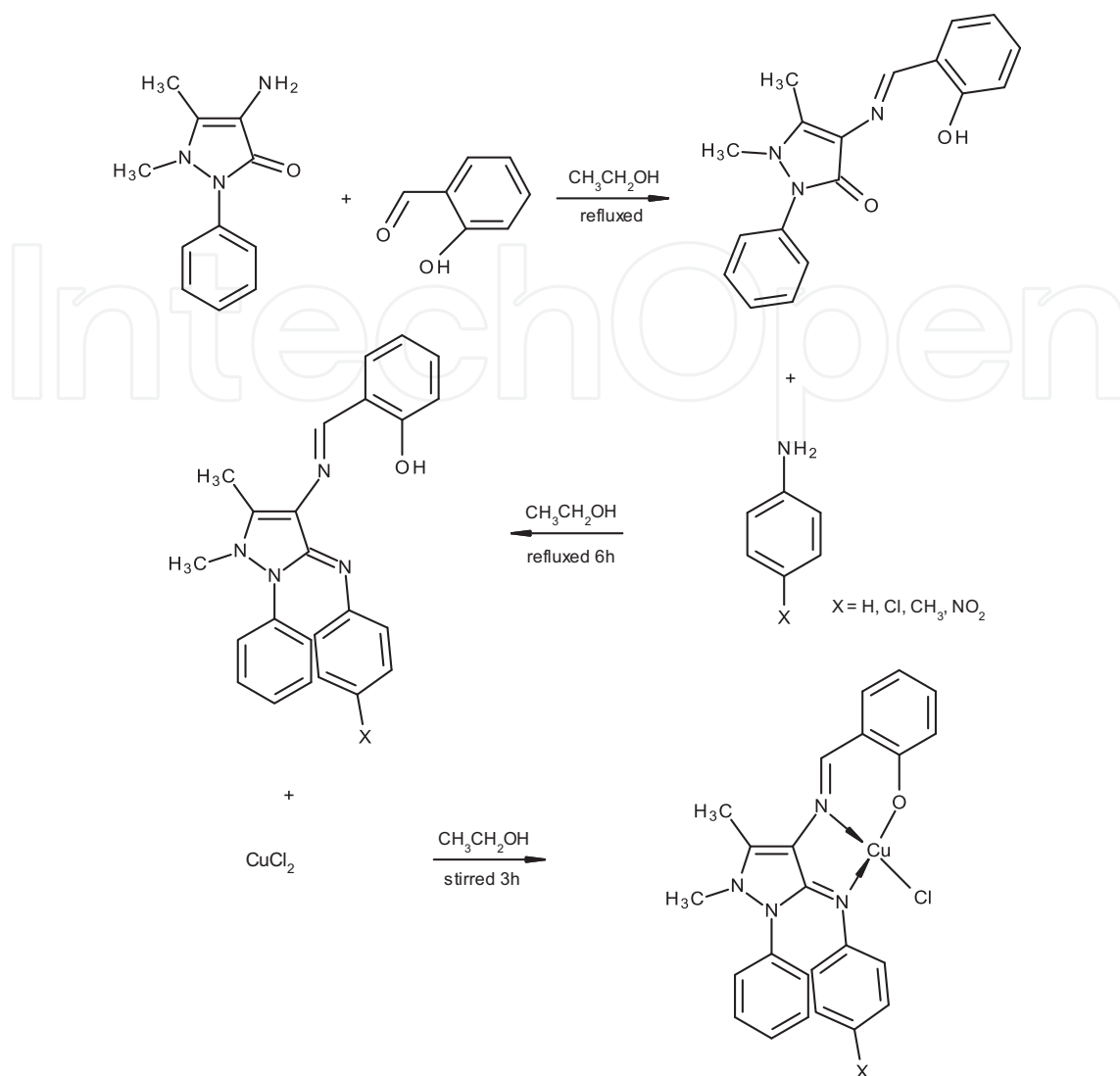
The study methods used to describe the complexes were as follows: the basic chemical analysis, spectrometry IR, UV-VIS, EPR, the thermogravimetric analysis, the magnetic susceptibility, and the molar electric conductivity. The complexes synthesized were tested from the point of view of the antibacterial activity; the obtained results were presented in the respective papers.

## 2.2. New compounds: structure and antibacterial activity

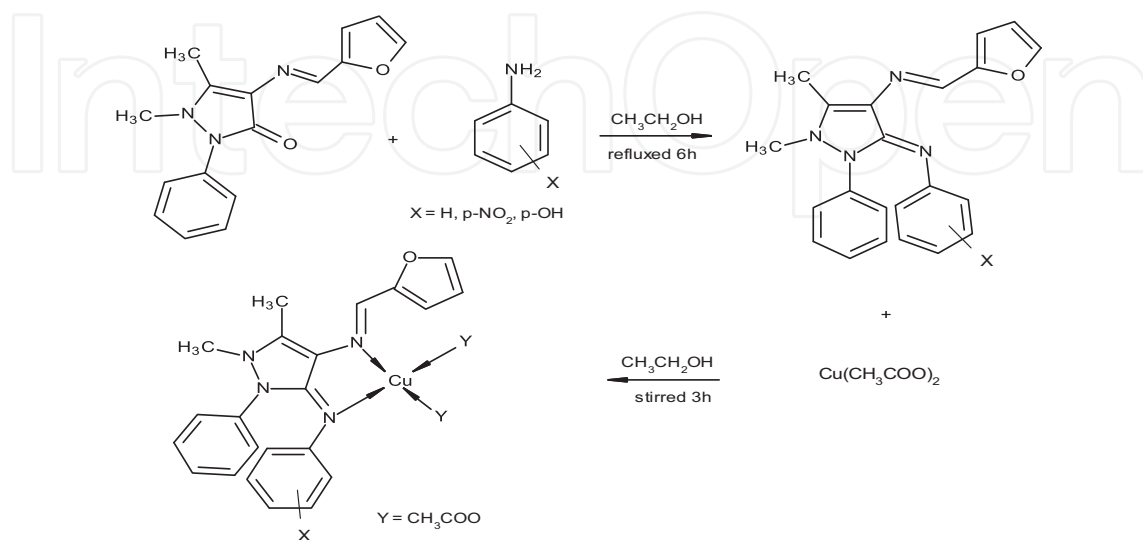
### 2.2.1. Structure and synthesis of the compounds 1–28

With a view to obtaining new compounds with significant antibacterial activity, we have synthesized and characterized a series of complexes of  $\text{Cu}(\text{II})$ ,  $\text{Ni}(\text{II})$ ,  $\text{Mn}(\text{II})$ , and  $\text{V}(\text{IV})$  with ligands Schiff bases, derived from 4-aminoantipyrine.

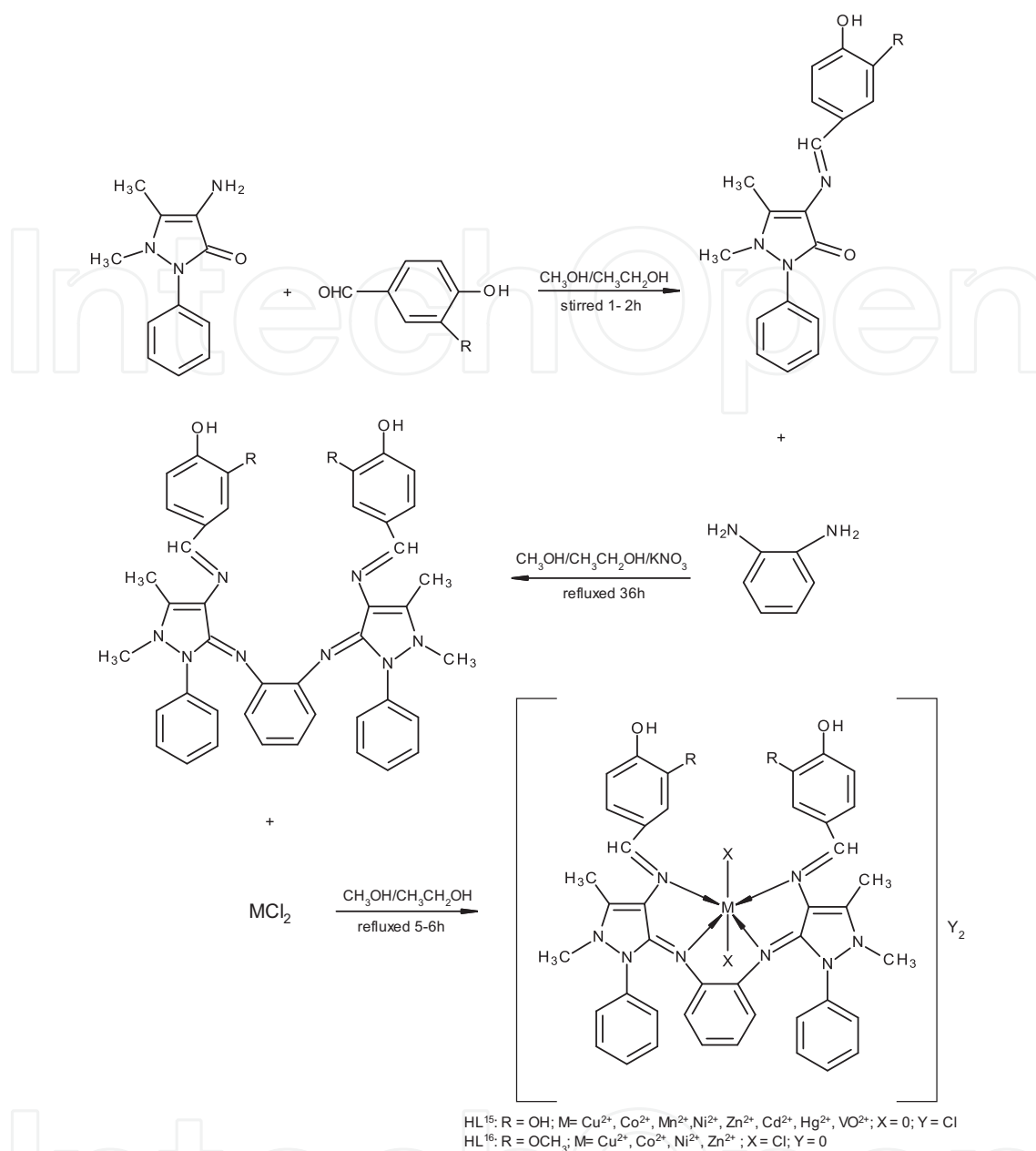
In this regard, we have synthesized four ligands, with chromophore groups ONO, respectively, ON, and different volumes of the aldehyde which is a part of Schiff base: 1-phenyl-2,3-dimethyl-4-(N-3-formyl-6-methyl-chromone)-3-pyrazolin-5-one (**HL<sup>21</sup>**); 1-phenyl-2,3-dimethyl-4-(N-2-hydroxy-4-methoxy-benzaldehyde)-3-pyrazolin-5-one (**HL<sup>22</sup>**); 1-phenyl-2,3-dimethyl-4-(1H-indole-3-carboxaldehyde)-3-pyrazolin-5-one (**HL<sup>23</sup>**); 1-phenyl-2,3-dimethyl-4-(N-pyridoxal hydrochloride)-3-pyrazolin-5-one (**HL<sup>24</sup>**) as well as their complex combinations with transitional metals:  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{VO}^{2+}$  (28 metal complexes).



**Figure 9.** Scheme of synthesis of complexes with ligand **HL**<sup>12</sup>.



**Figure 10.** Scheme of synthesis of complexes with ligand **HL**<sup>10</sup>.



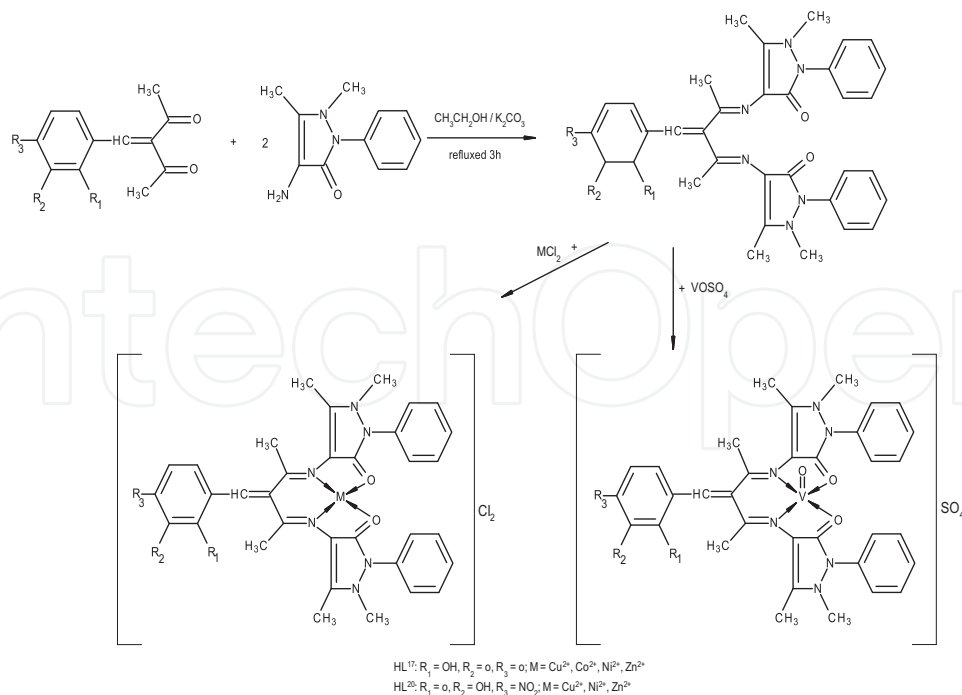
**Figure 11.** Scheme of synthesis of complexes with ligands HL<sup>15</sup> and HL<sup>16</sup>.

The study methods used to characterize the metal complexes were as follows: elemental analysis, the thermogravimetric analysis, IR, UV-Vis, EPR spectroscopy, the molar electric conductivity, the magnetic susceptibility, and the X-ray diffraction.

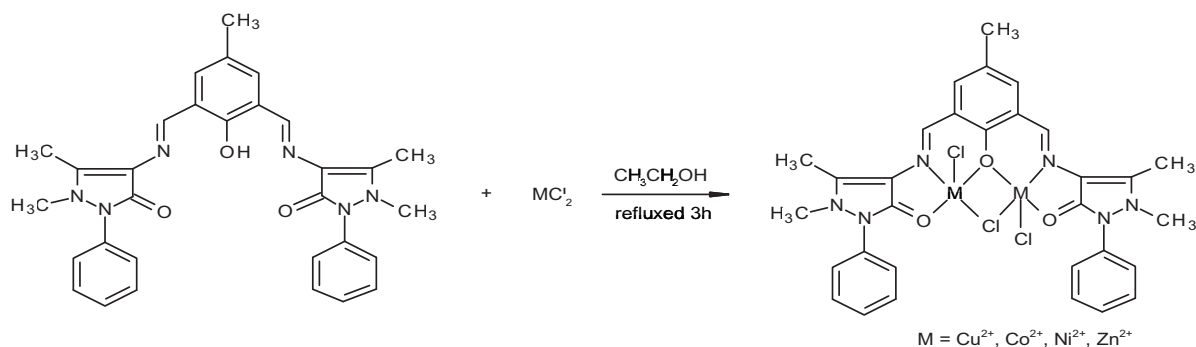
#### 2.2.1.1. Synthesis of the complexes with ligand HL<sup>21</sup>

##### Ligand C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>, (HL<sup>21</sup>)

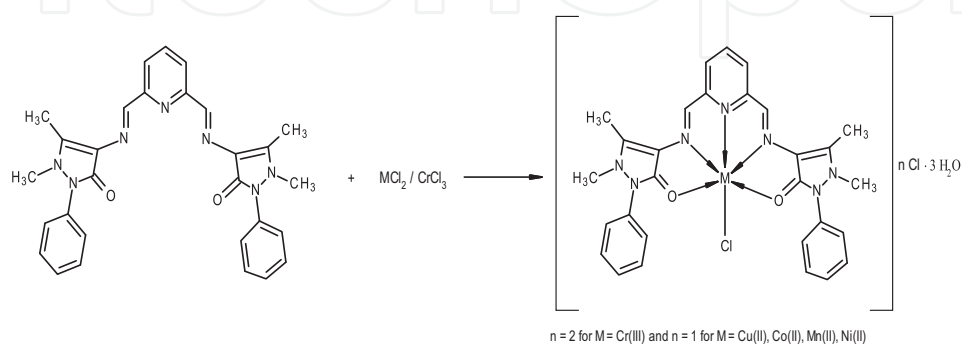
Ethanol solution of 3-formyl-6-methyl-chromone (1 mmol) and 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1 mmol) was stirred at room temperature, then refluxed for 2h, and kept at



**Figure 12.** Scheme of synthesis of complexes with ligands HL<sup>17</sup> and HL<sup>20</sup>.



**Figure 13.** Scheme of synthesis of complexes with ligand HL<sup>18</sup>.



**Figure 14.** Scheme of synthesis of complexes with ligand HL<sup>19</sup>.

4°C for 2 days. The resulting precipitate of intense yellow color was filtered, washed with methanol, and dried. Yellow single crystals suitable for structure determination were obtained from methanolic solution upon slow evaporation at room temperature [65].

Complexes **1–3** and **5–9** were prepared by direct reaction between the ligand and the corresponding metal salts, while complex **4** was prepared by the metathetical displacement of the acetate ion, in  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ , by the thiocyanate ion [65] (**Figures 15, 16**).



To  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2 mmol) dissolved in aqueous/ethanol solution (1:2 v/v) was added ligand **HL**<sup>21</sup> (2 mmol) dissolved in hot ethanol and refluxing for 2 h. The green-brown precipitate, which separated on cooling, was filtered, washed with hot water, ethanol followed by ether, and dried in vacuo.



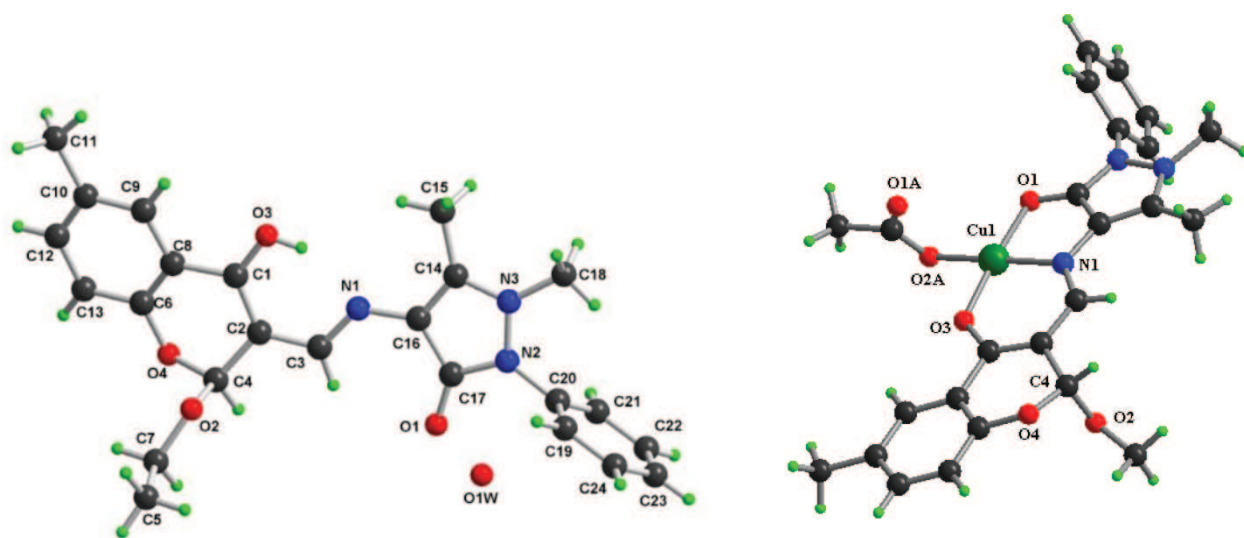
Complex **2** was prepared similarly, using  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (2 mmol). Green solid.



Complex **3** was prepared similarly, using  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (2 mmol). Brown solid, X-ray quality single crystals were obtained.



For the synthesis of complex **4**, the acetate complex was first prepared and the acetate ion was then displaced by thiocyanate ion by using KSCN (2 mmol). Dark-green solid.



**Figure 15.** X-ray molecular structure of ligand **HL**<sup>21</sup> and complex **3**.

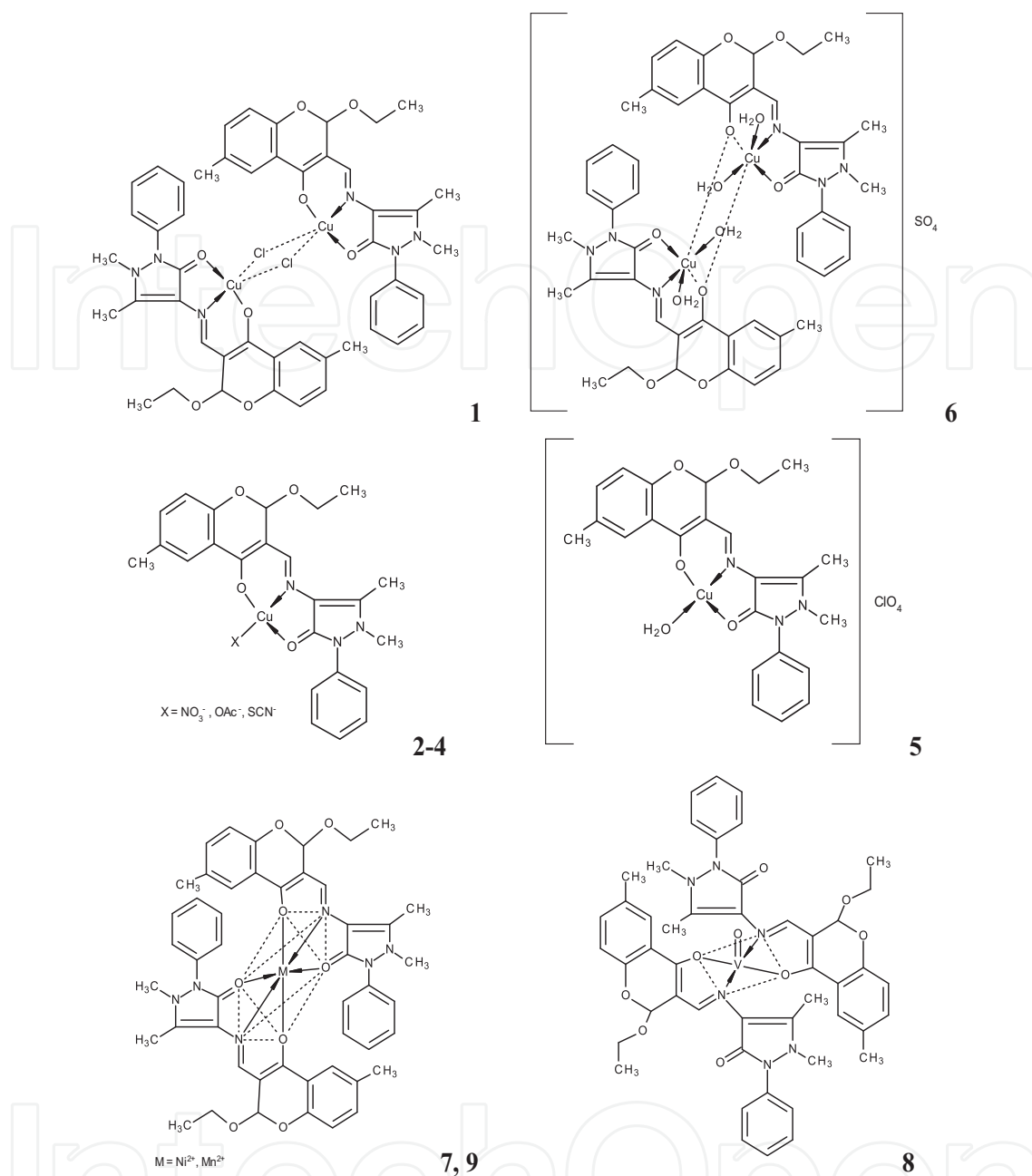


Figure 16. Proposed structures of the metal complexes 1-9.



Complex 5 was prepared similarly, using  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2 mmol). The mixture was stirred at room temperature for 1 h, when a dark-green precipitate appeared immediately.



Complex 6 was prepared similarly, using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (2 mmol). The mixture was stirred at reflux temperature for 4 h, when appeared a dark-green precipitate.



Complex **7** was prepared similarly, using  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (2 mmol). Green to yellow solid.



Complex **8** was prepared similarly, using  $\text{VOSO}_4 \cdot 2\text{H}_2\text{O}$  (2 mmol). Brown solid.



Complex **9** was prepared similarly, using  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2 mmol). Orange solid.

#### 2.2.1.2. Synthesis of the complexes with ligand $\text{HL}^{22}$

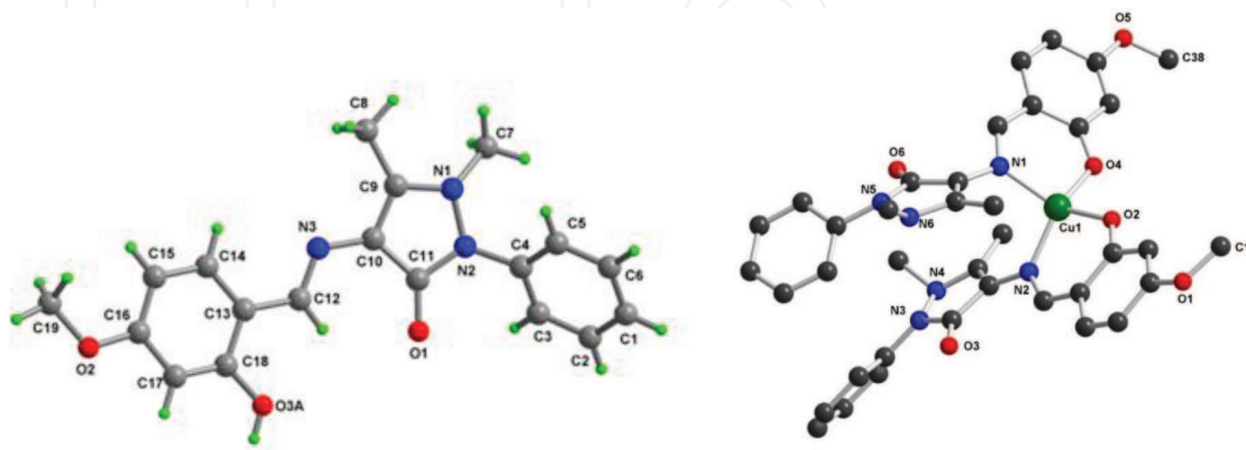
##### Ligand $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3$ , ( $\text{HL}^{22}$ )

The ligand  $\text{HL}^{22}$  was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 2-hydroxy-4-methoxy-benzaldehyde in ethanol according to the experimental protocol described in Ref. [66].

Complexes **10–12**, **14**, and **15** were prepared by the direct reaction between the ligand and the corresponding metal salts. Complex **13** was obtained by refluxing a mixture of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  and 1-phenyl-2,3-dimethyl-4-(N-2-hydroxy-4-methoxy-benzaldehyde)-3-pyrazolin-5-one with the addition of KSCN (**Figures 17, 18**) [66].

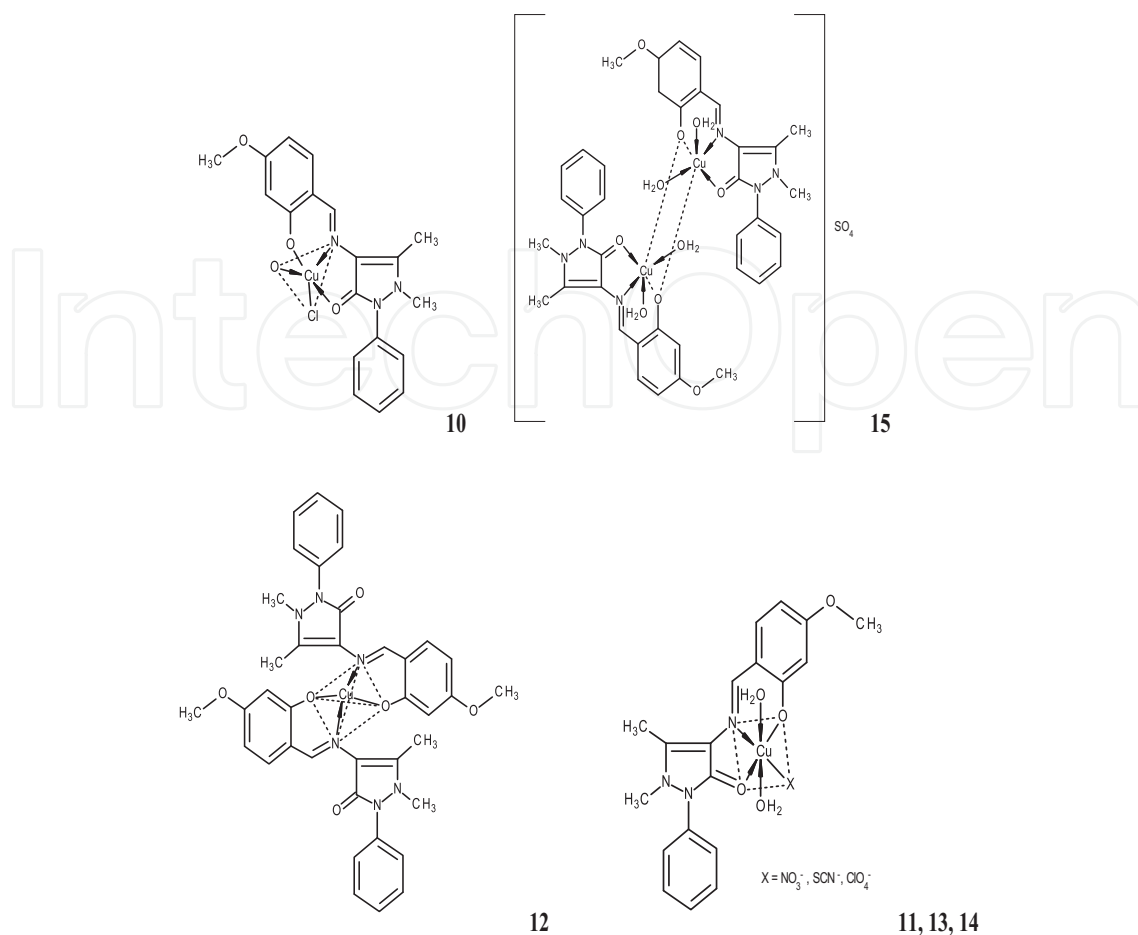


An ethanol solution of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2 mmol, 15 mL aqueous/ethanol 1:2 v/v) was added dropwise to a stirred ethanol solution of the Schiff base ligand  $\text{HL}^{22}$  (2 mmol, 15 mL). The resulting solution was stirring for 3 h at room temperature. The green-brown colored solid was filtered, washed with hot water, ethanol followed by ether, and dried in vacuo.

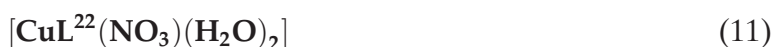


**Figure 17.** X-ray molecular structure of ligand  $\text{HL}^{22}$  and complex **12**.





**Figure 18.** Proposed structures of the metal complexes 10–15.



Complex **11** was prepared similarly, using  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (2mmol). Dark-green solid.



Complex **12** was prepared similarly, using  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (2mmol). Brown solid, X-ray quality single crystals were obtained.



For the synthesis of complex **13**, the chloride complex was first prepared and chloride ion was then displaced by thiocyanate ion by using KSCN (2mmol). The green colored solid, which separated on cooling, were filtered, washed with hot water, ethanol followed by ether and dried in vacuo.



Complex **14** was prepared similarly, using  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2mmol). Green solid.



Complex **15** was prepared similarly, using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (2 mmol). Dark-green solid.

### 2.2.1.3. Synthesis of the complexes with ligand $\text{HL}^{23}$

#### Ligand $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}$ , ( $\text{HL}^{23}$ )

The ligand  $\text{HL}^{23}$  was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and indole-3-carboxaldehyde in methanol according to the experimental protocol described in Ref. [67].

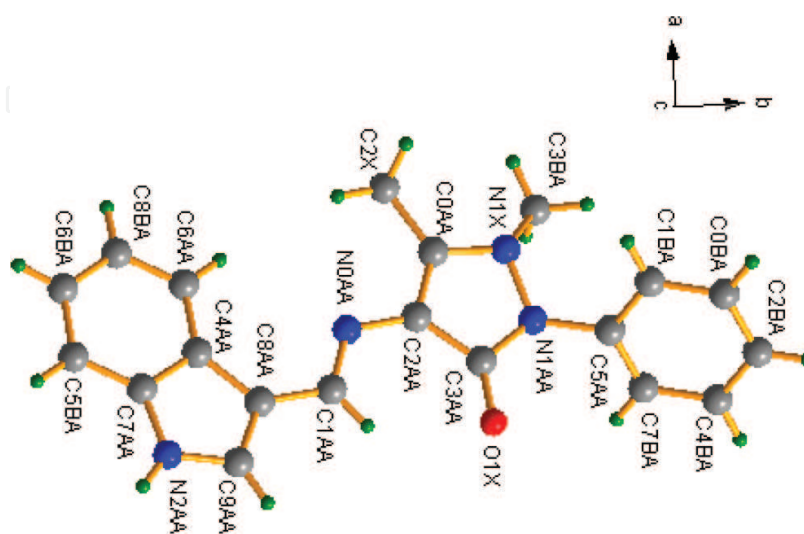
Complexes **16–21** were prepared by direct reaction between the ligand and the corresponding metal salts (**Figures 19, 20**) [67].



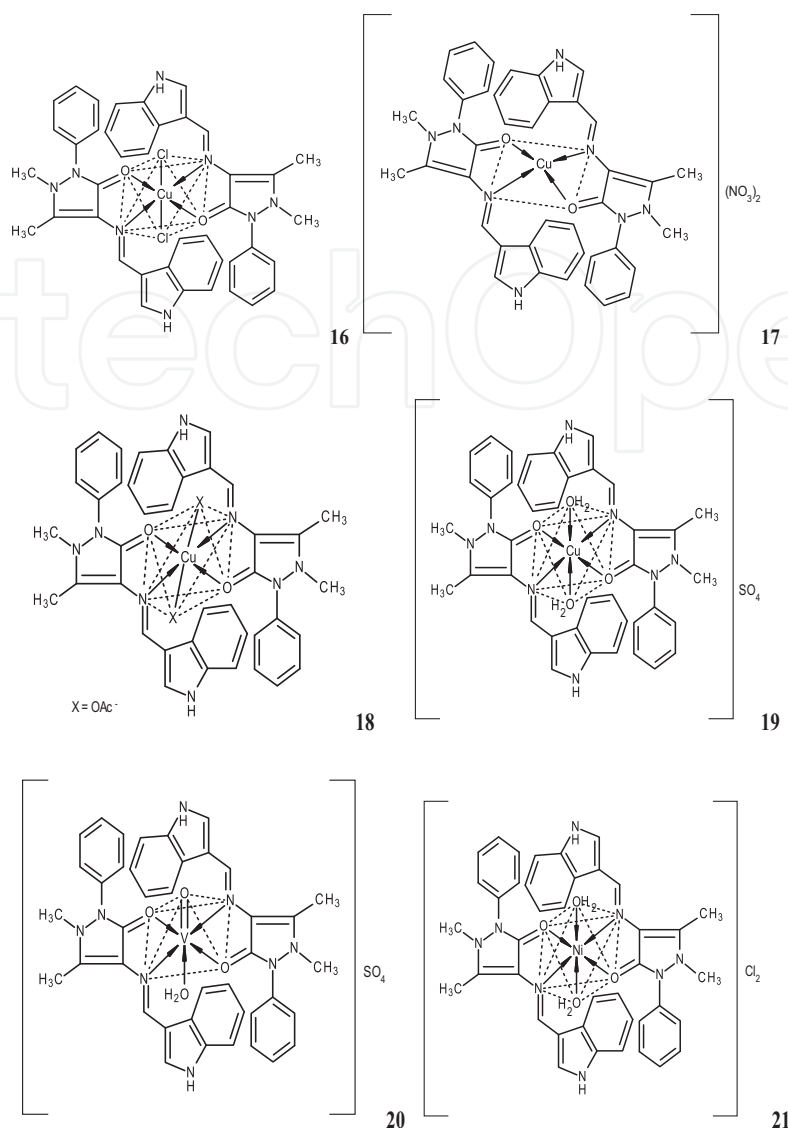
To a stirred solution of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (1 mmol) in ethanol (15 mL) was added a solution of ligand  $\text{HL}^{23}$  (1 mmol) in ethanol (15 mL). The mixture was stirred at reflux temperature for 2 h. The resulting precipitate of green-brown color was filtered, washed with ethanol, and dried.



Complex **17** was prepared similarly, using  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (1 mmol). Brown solid.



**Figure 19.** X-ray molecular structure of ligand  $\text{HL}^{23}$ .



**Figure 20.** Proposed structures of the metal complexes 16–21.

Complex **18** was prepared similarly, using Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 mmol). Dark-green solid.



Complex **15** was prepared similarly, using CuSO<sub>4</sub>·5H<sub>2</sub>O (1 mmol). Green solid.



Complex **20** was prepared in a similarly, using VOSO<sub>4</sub>·2H<sub>2</sub>O. Green solid.



Complex **21** was prepared in a similarly, using NiCl<sub>2</sub>·6H<sub>2</sub>O. Dark-green solid.

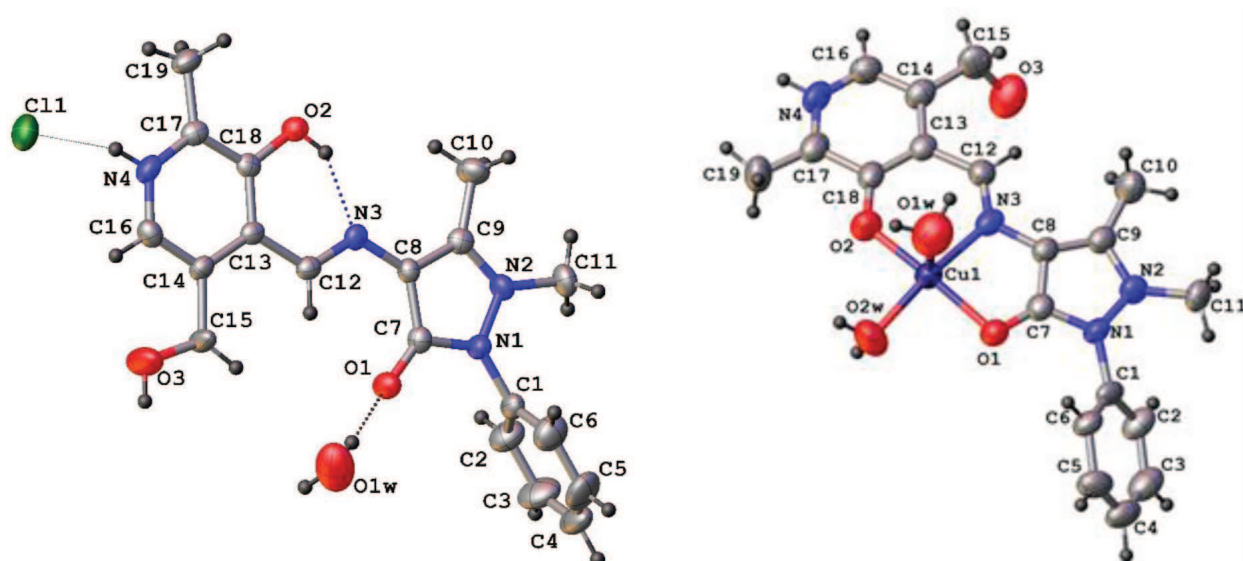


Figure 21. X-ray molecular structure of ligand  $\text{HL}^{24}$  and complex 23.

#### 2.2.1.4. Synthesis of the complexes with ligand $\text{HL}^{24}$

##### Ligand $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_3$ , ( $\text{HL}^{24}$ )

The ligand  $\text{HL}^{24}$  was synthesized by refluxing equimolar amounts of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and pyridoxal hydrochloride in methanol according to the experimental protocol described in Ref. [68].

Complexes **22–28** were prepared by direct reaction between the ligand and the corresponding metal salts (**Figures 21, 22**) [68].



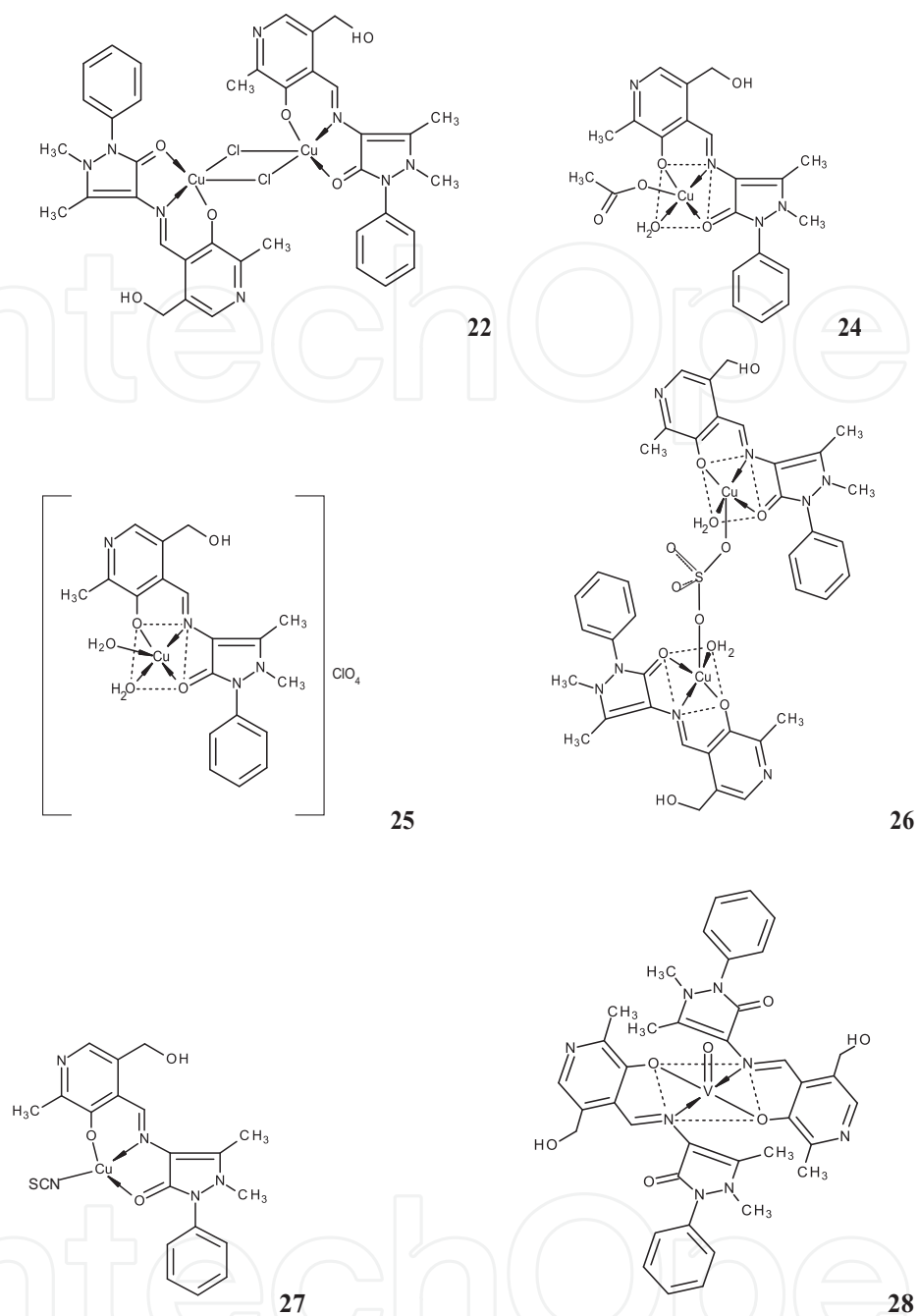
To a hot solution of  $\text{HL}^{24}$  (1 mmol) in methanol was added a hot solution of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (2 mmol) in aqueous/methanol (1:2 v/v), and the mixture was stirred at reflux temperature for 4 h. Brown solid.



Complex **23** was prepared similarly, using  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (1 mmol). The mixture was stirred at room temperature for 7 h. Brown solid, X-ray quality single crystals were obtained.



Complex **24** was prepared similarly, using  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (2 mmol). The mixture was stirred at reflux temperature for 4 h. Green-brown solid.



**Figure 22.** Proposed structures of the metal complexes 22, 24–28.



Complex **25** was prepared similarly, using  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (2mmol). The mixture was stirred at reflux temperature for 5h. Brown solid.



Complex **26** was prepared in a similar fashion to complex **24**, using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ . The mixture was stirred at reflux temperature for 4h, giving a dark-red precipitate.



For the synthesis of complex **27**, the acetate complex was first prepared and the acetate ion was then displaced by thiocyanate ion by using KSCN (2mmol). Green solid.



Complex **28** was prepared in a similar fashion to complex **24**, using  $\text{VO}(\text{SO}_4)_2 \cdot 2\text{H}_2\text{O}$ . Brown solid.

### 2.3. Antibacterial activity

The complexes and ligands  $\text{HL}^{21-24}$  were tested for their in vitro antibacterial activity against *Staphylococcus aureus* var. Oxford 6538, *Klebsiella pneumoniae* ATCC 100131, *Escherichia coli* ATCC 10536, and *Pseudomonas aeruginosa* ATCC 9027 strains using the paper disc diffusion method (for the qualitative determination) and the serial dilutions in liquid broth method (for determination of MIC) [66]. Streptomycin was used as internal standard.

The results of the antibacterial activity point out the fact that the activity of the Schiff bases  $\text{HL}^{21-24}$  is more pronounced when it coordinates at the metal ion (Table 1). In case of complexes **1**, **6**, **10**, **12**, **15**, **18**, **19**, **20**, **23**, **25**, **26**, and **28**, there can be seen a visible increase in the antibacterial action.

Missing a clear action mechanism, in vitro, of the respective ligand of the complexes obtained on a microbial stem, there can be made the following stipulations:

- the structure of the tested complexes seems to be the main element that influences the antibacterial activity. Thus, for complexes **1**, **6**, **10**, **12**, **15**, **19**, **20**, **23**, **25**, **26**, and **28**, there has been determined an increased activity against all bacterial species, probably due to the presence of the monomeric form in DMSO solution and also due to the tetracoordination of the metal center.

- the presence of the anions with a large volume, in the outer coordination sphere of the complexes, can be deemed as another main element that can influence the antibacterial activity. The complexes **5**, **6**, **15**, **19**, **20**, and **25** contain the groups  $\text{ClO}_4^-$  and  $\text{SO}_4^{2-}$ , respectively, and prevent a visible increase in their activity against all species of bacteria used.

- if there is drawn a comparison between the coefficients of the molecular orbitals, computed on the basis of the transitions noticed in spectra UV-Vis and of the parameters  $g$  and  $A$  in spectra EPR [69] and the antibacterial activity, the conclusion is the fact that, for the complexes with the most pronounced activity, the values of  $\delta^2$  parameter to a weak covalent character of the link  $\pi$  out of the plan.

Compusul	Minimum inhibitory concentration (µg/ml)			
	<i>K. pneumoniae</i> G(+)	<i>S. aureus</i> G(+)	<i>P. aeruginosa</i> G(–)	<i>E. coli</i> G(–)
<b>HL<sup>21</sup></b>	256	256	512	128
[Cu <sub>2</sub> (L <sup>21</sup> ) <sub>2</sub> (Cl) <sub>2</sub> ] ( <b>1</b> )	32	8	32	32
[CuL <sup>21</sup> (NO <sub>3</sub> )] ( <b>2</b> )	64	32	256	512
[CuL <sup>21</sup> (OAc)] ( <b>3</b> )	64	32	256	512
[CuL <sup>21</sup> (SCN)] ( <b>4</b> )	64	32	256	512
[CuL <sup>21</sup> (H <sub>2</sub> O)]ClO <sub>4</sub> ( <b>5</b> )	32	32	128	256
[Cu <sub>2</sub> (L <sup>21</sup> ) <sub>2</sub> (H <sub>2</sub> O) <sub>4</sub> ]SO <sub>4</sub> ( <b>6</b> )	16	8	32	32
[Ni(L <sup>21</sup> ) <sub>2</sub> ] ( <b>7</b> )	512	512	256	512
[VO(L <sup>21</sup> ) <sub>2</sub> ] ( <b>8</b> )	265	256	64	256
[Mn(L <sup>21</sup> ) <sub>2</sub> ] ( <b>9</b> )	256	512	256	128
<b>HL<sup>22</sup></b>	128	256	256	512
[Cu(L <sup>22</sup> )Cl(H <sub>2</sub> O)] ( <b>10</b> )	16	8	128	16
[Cu(L <sup>22</sup> )(NO <sub>3</sub> )(H <sub>2</sub> O) <sub>2</sub> ] ( <b>11</b> )	128	128	256	256
[Cu(L <sup>22</sup> ) <sub>2</sub> ] ( <b>12</b> )	8	4	16	64
[CuL <sup>22</sup> (SCN)(H <sub>2</sub> O) <sub>2</sub> ] ( <b>13</b> )	64	64	256	512
[CuL <sup>22</sup> (ClO <sub>4</sub> )(H <sub>2</sub> O) <sub>2</sub> ] ( <b>14</b> )	256	128	256	512
[Cu <sub>2</sub> (L <sup>22</sup> ) <sub>2</sub> (H <sub>2</sub> O) <sub>4</sub> ]SO <sub>4</sub> ( <b>15</b> )	8	16	128	16
<b>HL<sup>23</sup></b>	64	128	64	32
[Cu(L <sup>23</sup> ) <sub>2</sub> Cl <sub>2</sub> ] ( <b>16</b> )	64	128	64	64
[Cu(L <sup>23</sup> ) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub> ( <b>17</b> )	128	64	32	64
[Cu(L <sup>23</sup> ) <sub>2</sub> (OAc) <sub>2</sub> ] ( <b>18</b> )	8	4	16	16
[Cu(L <sup>23</sup> ) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]SO <sub>4</sub> ( <b>19</b> )	8	8	64	16
[VO(L <sup>23</sup> ) <sub>2</sub> (H <sub>2</sub> O)]SO <sub>4</sub> ( <b>20</b> )	64	128	16	256
[Ni(L <sup>23</sup> ) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]Cl <sub>2</sub> ( <b>21</b> )	256	256	256	128
<b>HL<sup>24</sup></b>	128	256	256	512
[CuL <sup>24</sup> Cl] <sub>2</sub> ( <b>22</b> )	64	64	256	512
[CuL <sup>24</sup> (H <sub>2</sub> O) <sub>2</sub> ]NO <sub>3</sub> ·2.25H <sub>2</sub> O ( <b>23</b> )	16	8	128	16
[Cu(L <sup>24</sup> )(OAc)(H <sub>2</sub> O)] ( <b>24</b> )	128	128	256	256
[CuL <sup>24</sup> (H <sub>2</sub> O) <sub>2</sub> ] ClO <sub>4</sub> ( <b>25</b> )	8	4	16	64
[Cu <sub>2</sub> (L <sup>24</sup> ) <sub>2</sub> (SO <sub>4</sub> )(H <sub>2</sub> O) <sub>2</sub> ] ( <b>26</b> )	8	64	16	64
[CuL <sup>24</sup> (NCS)]·2H <sub>2</sub> O ( <b>27</b> )	256	128	256	512
[VO(L <sup>24</sup> ) <sub>2</sub> ] ( <b>28</b> )	8	16	128	16
Streptomycin	8	4	16	8

*K. pneumoniae* (*Klebsiella pneumoniae* ATCC 31488); *S. aureus* (*Staphylococcus aureus* var. Oxford ATCC 6538); *P. aeruginosa* (*Pseudomonas aeruginosa* ATCC 9027); *E. coli* (*Escherichia coli* ATCC 10536). G(–): Gram-negative bacteria; G(+): Gram-positive bacteria.

**Table 1.** “In vitro” antibacterial activity of the ligands and corresponding complexes.



### 3. Conclusion

The investigations of the antibacterial screening, carried out for these new classes of compounds, reveal the fact that they present activity, especially toward the gram-positive bacteria, in comparison with the standard streptomycin. The increased antibacterial activity of the metal complexes can be accounted for by a cluster of reasons that refer to the chelation theory, nature of the ligand and of the metal ion, the geometry of the metal complexes, liposolubility, the presence of the co-ligands, and a series of sterical and pharmacokinetic factors. We can say that, ten of the complexes synthesized can be successfully used instead of streptomycin, where there is resistance to this antibiotic.

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